Prospective, comparative study for the evaluation of lymph node involvement in gastric cancer: Maruyama computer program versus sentinel lymph node biopsy

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Abstract

Background Stage-adapted surgery guarantees the best outcome for patients with gastric cancer. Successful identification of lymph node involvement may help to reduce the number of extended lymphadenectomies. Preoperative diagnostic tools have low sensitivity and specificity for determining lymph node involvement. Evaluation of sentinel lymph nodes (SLNs) intraoperatively has good results, while the accuracy of the Maruyama computer program (MCP) is controversial.

Methods We investigated 40 patients by the Maruyama computer model and labeled lymph nodes with blue dye for SLN mapping. To compare the probability calculations by MCP and the results of SLN mapping, we had to define a cutoff level; we did this using receiver-operating characteristics analysis. Sentinel lymph nodes were examined in frozen sections intraoperatively and by standard hematoxylin and eosin staining postoperatively.

Results A total of 795 lymph nodes were removed and examined. The Maruyama computer model had a sensitivity of 91.3 %, specificity of 64 %, and accuracy of 80 %

by the best cutoff point. The false-negative rate was 8.7 %. The sensitivity of SLN mapping was 95.7 %, the false-negative rate was 4.3 %, and the specificity was 100 %. The accuracy of SLN mapping was 97.4 %. Only the sensitivity of MCP and SLN biopsy was proven equivalent. **Conclusions** Our results suggest that intraoperative SLN examination is superior to preoperative estimation with the MCP. Correct definition of lymph node involvement helps in planning the best stage-adapted surgery in gastric cancer.

Keywords Gastric cancer · Maruyama computer program · Sentinel lymph node biopsy · Sensitivity and specificity

Introduction

The presence of lymph node metastases is the most important predictive factor for survival in gastric cancer in patients with potentially curative resection [1, 2]. More than one-third of patients with gastric adenocarcinoma have an unnecessarily extended lymph node dissection [3]. Several studies have shown increased perioperative morbidity and mortality with D2 versus D1 lymph node dissection [4–6]. Successful estimation of lymph node involvement may help to define those patients who would and those who would not benefit from an extended lymph node dissection in association with gastrectomy. For this purpose, a computer program was developed by Maruyama and his colleagues [7] to estimate the incidence of lymph node metastases, the expected prognosis, and the proportion of curable cases at surgery, based on the most significant preoperative prognostic factors. This program was later improved as the Windows-based program WinEstimate v. 2.5, using a database of 4302 primary gastric

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Fig. 1 Prediction of lymph node involvement by the Maruyama computer program in a 53-year-old female patient. The tumor histology was moderately differentiated adenocarcinoma, showing definite serosal involvement (S2), Borrmann type 3. The lesion was found in the anterior wall in the lower third of the stomach and had a maximal diameter of 15 mm

cancer patients treated at the National Cancer Center Hospital in Tokyo between 1968 and 1989 [8].

Sentinel lymph node (SLN) mapping has become a standard procedure in breast cancer and malignant melanoma [9, 10]. The injection method and selection of tracers for SLN mapping in gastric cancer remain controversial. Studies from Japan and from Western Europe have demonstrated a high detection rate (93.7 %) and an accuracy of 92 % for SLN biopsy in patients with gastric cancer [11]. We have evaluated, for the first time in Hungary, the validity of SLN mapping using a blue dye-only method in gastric cancer [12].

In this prospective study we compared the efficacy of the Maruyama computer program (MCP) and the SLN biopsy (SNB) technique to predict the nodal status and localization of lymph node metastases in our patients.

Patients, materials, and methods

The study was conducted prospectively from February 2008 to April 2011, at the Department of Surgery of the Gyula Kenézy Teaching County Hospital, Debrecen, Hungary. Exclusion criteria were gastric stump tumor, cardia cancer, distant metastases, and involvement of the surrounding organs (T4). Forty consecutive patients were evaluated with the MCP. The calculation required the following prognostic factors in every patient: age, gender, position of the tumor (upper, middle, or lower third of the stomach, anterior or posterior wall, lesser or greater curvature), Borrmann's classification or early gastric cancer classification according to the Japanese Endoscopy Society, depth of infiltration, and histological type. Based on these data, the computer model calculated the proportion of

Fig. 2 Sentinel lymph node subserosal mapping with blue dye only. This photograph shows good labeling of the lymphatic vessel and lymph node station 3

supposedly positive nodes at each lymph node location (stations 1–16) (Fig. 1).

All the patients underwent open gastric resection with blue dye mapping (Fig. 2) and modified D2 lymph node dissection (stations 1 and 2 in patients with total gastrectomy and stations 3–9, 11, and 12 routinely). Sampling of station 10 and compartment 3 nodes (13–16) was optional if macroscopically suspicious, so we did not routinely calculate the values of these stations. Our SLN marking method and the histological examination were described earlier [12]. The position of lymph nodes was labelled according to the *Japanese classification of gastric carcinoma* (JCGC) [13]. Only negative sentinel nodes were examined for micrometastases. Postoperatively, the SLNs

were sectioned at 0.2-mm intervals and hematoxylin and eosin (HE) staining was performed, and immunohistochemistry examinations were performed with DAKO Monoclonal Mouse Anti-Human Cytokeratin (clone AE1/AE3; dilution 1:30; Dakocytomation; Glostrup; Denmark).

To compare the probability calculations by MCP and the results of SLN mapping, we had to define a cutoff level; this was done using receiver-operating characteristics (ROC) analysis [14]. This logistic regression model indicates the probability of concordance between the predicted probability and the proven diagnosis of lymph node metastasis. We estimated the sensitivity and specificity with several cutoff points of the Maruyama program for the expected percentage values obtained by the ROC analysis for each of the 12 lymph node (LN) stations. We defined the best cutoff points for every LN station and the common critical cutoff point to maximize the test validity.

For each station, we declared positivity if its Maruyama value was greater than or equal to the cutoff specific to that station. Overall positivity was then declared based on the presence of station-specific positivity at any station included in the analysis. Thus, the only way for station elimination to produce a difference is if positive stations are eliminated such that all remaining stations are negative.

Statistical analysis of equivalence between the results of MCP and SLN mapping was based on calculating the ratios of test performance indicators (those of the SLN mapping method divided by those of the MCP procedure). Equivalence was established when the 95 % exact confidence interval around such a ratio was fully contained within the range 0.8–1.25.

The statistical package Stata [15] was used for data handling and analysis. Confidence intervals based on robust standard errors were calculated by using the Variance-Covariance matrix of the Estimators (cluster (clustervar)) option in a Poisson regression model formulated for the relative comparison of two proportions, where (clustervar) denotes the subject identifier, i.e., a variable taking the same unique value in the two records (one for Maruyama-based, and another for sentinel LN-based results) for each subject. The option is made available in Stata explicitly for the analysis of datasets of a multiple-observations-per-subject structure and produces robust, rather than naïve, standard errors based on the Huber–White (sandwich) estimator of variance [16] generalized and implemented for the purpose [17].

Results

We investigated 40 consecutive patients, 21 females and 19 males with a mean age of 64.1 (range 50–80) years. The average body mass index (BMI) was 22.6 (range

17.1–27.6). Fifteen patients had signet-ring cell carcinoma, 18 patients had moderately differentiated adenocarcinoma, and 7 patients had poorly differentiated adenocarcinoma. The tumor was localized in the upper third of the stomach in 8 patients, in the middle third of the stomach in 10 patients, and in the lower third of the stomach in 22 patients. The depth of invasion was T1 in 10, T2 in 11, and T3 in 19 patients. Total gastrectomy was performed in 14 patients, and subtotal gastrectomy in 26 patients. A total of 795 lymph nodes were removed, and 19.9 lymph nodes per patient were examined on average (range 10–38 lymph nodes per patient). The mean number of blue nodes was 4.25 per patient. The frequency of lymph node labeling was evaluated in relation to the tumor's location (Table 1). In two patients with a lower-third tumor the lymph node station 10 was labeled in an uncommon manner. Both patients had a circular tumor. The first patient had a T3, grade 3, papillary adenocarcinoma with lymphatic vessel invasion, and five lymph nodes were labeled (LN no. 3, no. 6, no. 7, no. 8, and no. 10), while the other patient had a T3, grade 3, signet-ring cell carcinoma and twelve lymph nodes were stained (LN no. 5, no. 6, no. 7, no. 8, no. 10, no. 11, and no. 12).

Table 2 shows the frequency of patients with dissected LN stations and metastatic involvement.

The best cutoff point was estimated for every LN station and a critical cutoff point of 12 % of the MCP expected percentage maximized the test validity (Table 2). In 2 patients with metastases in LN stations 9 and 12 the MCP was calculated as 0 %, so the sensitivity was zero with any cutoff level, as it was in 2 other patients with metastases in LN station 10.

The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of MCP were calculated with a 12 % cutoff point and the best cutoff point station by station (Table 3).

Table 1 Frequency of lymph node (LN) labeling in relation to tumor location

LN station	Upper third (<i>N</i> = 8)	Middle third (<i>N</i> = 9)	Lower third (<i>N</i> = 22)
1	2 (25 %)	6 (67 %)	2 (9 %)
3	4 (50 %)	4 (44 %)	12 (54 %)
4	0 (0 %)	0 (0 %)	6 (27 %)
5	0 (0 %)	0 (0 %)	9 (41 %)
6	1 (12.5 %)	1 (11 %)	14 (63 %)
7	2 (25 %)	4 (44 %)	8 (36 %)
8	2 (25 %)	1 (11 %)	4 (18 %)
10	0 (0 %)	0 (0 %)	2 (9 %)
11	0 (0 %)	0 (0 %)	2 (9 %)
12	0 (0 %)	0 (0 %)	2 (9 %)

Table 2 Frequency of patients with dissected and metastatic LN stations

LN station ^a	Frequency of dissected LN station	Frequency of metastatic lymph nodes (no. of cases)	MCP percent cutoff points	Area under the ROC curve	Sensitivity (%)	Specificity (%)
1	15/40 (37.5 %)	6	6	0.765	100	52.9
			12	0.627	66.7	58.8
2	14/40 (35 %)	2	12	0.447	0	89.5
3	38/40 (95 %)	14	12	0.602	85.7	34.6
			18	0.640	85.7	42.3
4	36/40 (90 %)	8	12	0.516	50	53.1
			15	0.563	50	62.5
5	28/40 (70 %)	4	12	0.694	50	88.9
6	36/40 (90 %)	7	12	0.594	62.5	56.3
7	32/40 (80 %)	11	12	0.577	63.6	51.7
8	36/40 (90 %)	5	12	0.583	66.7	50
			15	0.672	66.7	67.6
9	29/40 (72.5 %)	2	12	0.289	0	57.9
			15	0.342	0	68.4
10	4/40 (10 %)	2	12	0.474	0	94.7
11	30/40 (75 %)	4	9	0.667	50	83.3
			12	0.417	0	83.3
12	30/40 (75 %)	2	12	0.368	0	73.7
			18	0.421	0	84.2

Estimated relation between given cutoff points (the best cutoff point and the 12% cutoff point) of MCP's expected percentage of LN positivity, and the corresponding statistical data (area under the ROC curve, sensitivity, and specificity) for each of 12 LN stations. The cutoff points for the best results are indicated in italics

LN lymph node, MCP Maruyama computer program, ROC receiver operating characteristic

^a Japanese classification of gastric carcinoma [13] numbering system

Table 3 Statistical features of MCP and SNB and the equivalency results

	MCP (12 % cutoff)	MCP (best cutoff)	SNB	Result (95 % CI)
Sensitivity	91.3	91.3	95.7	Equivalent
Specificity	52.9	64.7	100	Non-equivalent
ROC area	0.721	0.780	0.978	Non-equivalent
PPV	72.4	77.8	100	Non-equivalent
NPV	81.8	84.6	94.1	Non-equivalent
Accuracy	75	80	97.4	Non-equivalent

ROC receiver operating characteristic, PPV positive predictive value, NPV negative predictive value, MCP Maruyama computer program, SNB sentinel lymph node biopsy, CI confidence interval

In 39 patients SLNs were successfully identified, resulting in a detection rate of 97.5 %. Seventeen patients (42.5 %) were histologically node-negative; in 16 patients both SLNs and non-SLNs were negative. In one patient there was no sign of any labeling; the BMI of this patient was 26.8. In 22/23 patients at least one SLN showed tumor involvement, with a false-negative rate of 1/23 (4.3 %).

In this single false-negative case the tumor was T3 in extension, and grade 3 with perineural invasion histopathologically and macroscopically involved lymph nodes were found during the operation. In the sixteen SLN-negative cases micrometastases were not found in the sentinel nodes. The results of the intraoperative frozen sections (SLN) correlated completely with the postoperative pathological findings. Sensitivity was 95.7 %, and specificity was 100 %. The NPV was 94.1 % and the PPV was 100 %. The accuracy was 97.4 %.

Results of the MCP and SLN biopsies were equivalent only in sensitivity, based on the 95 % confidence interval (CI) of the ratio of performance indicators. Specificity, NPV, PPV, and accuracy with the SNB method were superior to those of MCP (Tables 3, 4).

The MCP with the best cutoff point (station by station) had a somewhat better statistical result than that with the 12 % cutoff point; however, the area under the curve value of SNB was higher. The difference was statistically significant between SNB and MCP with the 12 % cutoff point ($p = 0.0043$) and between SNB and MCP with the best cutoff point ($p = 0.0003$). The area under the curve value

Table 4 Ranges of 95 % confidence intervals

	MCP (12 % cutoff)/SNB	MCP (best cutoff)/SNB
Sensitivity	<i>0.812–1.122</i>	<i>0.812–1.122</i>
Specificity	0.334–0.840	0.451–0.929
PPV	0.576–0.910	0.633–0.955
NPV	0.642–1.177	0.694–1.165
Accuracy	0.635–0.934	0.693–0.972

The italicized values indicate equivalency. Criterion of equivalence: the 95 % confidence interval should be fully within the range 0.8–1.25

PPV positive predictive value, NPV negative predictive value, MCP Maruyama computer program, SNB sentinel lymph node biopsy

Fig. 3 Comparison of Maruyama computer model (12% cutoff and best cutoff) and sentinel lymph node biopsy by the area under the curve (AUC) of the receiver operating characteristic

of MCP with the best cutoff point was higher than that of MCP with the 12 % cutoff point, although the difference was not significant ($p = 0.1441$) (Fig. 3).

We evaluated the accuracy of MCP for the first tier lymph nodes, owing to the low value of the area under the ROC curve in stations 9, 10, and 12. However, the accuracy and the statistical features (sensitivity, specificity, PPV, NPV) did not change, because patients with false-negative second-tier lymph nodes had false-negative lymph nodes in the first tier also. The accuracy of MCP in sentinel node-positive patients was 91 % and it was only 75 % in the complete group of the forty patients.

The sensitivity of MCP in the cohort of SLN-positive patients was 91 % and the PPV was 100 %. So, these features of MCP and SNB were proven equivalent in the sentinel node-positive group. In these patients the specificity and NPV could not be defined, owing to the lack of sentinel node-negative patients.

The accuracy of the MCP for the prediction of lymph node metastasis in stations 7–12 was 50 % in sentinel

node-positive patients. This accuracy increased to 72 % when the sentinel node was found in compartment 2.

There were no side-effects of the blue dye mapping. The postoperative period was uneventful in all the 40 patients, without any surgical or nonsurgical complications.

Discussion

Dutch and British prospective randomized trials found higher morbidity and mortality rates in patients with gastric cancer following extended lymph node dissection when compared with findings for those who underwent D1 dissection only [4, 5]. Forty percent of Western European patients with R0 resection have an unnecessary extended lymph node dissection [3]. Preoperative diagnostic tools have low sensitivity and specificity for defining the patient subpopulations which would and which would not benefit from an extended lymph node dissection. The sensitivity, specificity, and accuracy of spiral computed tomography for the detection of pathological lymph node involvement are 73.1, 50.0, and 84.2 %, respectively [18] and endoscopic ultrasonography has an accuracy of 68.6 %, with a sensitivity and specificity of 66.7 and 73.7 %, respectively [19]. The real problem of these imaging procedures is that they look only at the size of lymph nodes; however, metastases can be found in small nodes as well, and conversely, large nodes may be metastasis-free.

To overcome this problem, the Maruyama computer model was developed, and it was first described in the English-language literature in 1989 [7]. The MCP calculates the probability (%) of lymph-node metastases for the different lymph-node positions 1–16, according to the JCGC. In Japanese patients, the program was able to predict lymph node involvement in 94 % [20]. In the European region the accuracy of the MCP was 91 % in Slovenian patients [21]. In Italian patients the accuracy was 83.4 % for stations 1–6 and 81.6 % for stations 7–12 [22]. The sensitivity for lymph node detection was high (97–100 %) in a German study of 222 patients, but specificity as low as 20 % was found for perigastric lymph nodes (stations 1–6) [23]. Similarly, in the Italian study, where the sensitivity was increased to 100 % with a lower cutoff level, the specificity dropped to 26 %. The false-positive rate was close to that in the German patients, but the false-negative rate was higher [22]. Better prediction of lymph node metastases may be feasible with an artificial neural network (ANN) using the following parameters: Bormann classification, depth of tumor infiltration, size, location of tumor, and lymph node metastases in station 3. With the ANN, accuracy increased from 66 to 93 % [24]. These studies demonstrate that, even if the sensitivity and the NPV are high, the specificity and the PPV of the

Maruyama model may be low. Still, the results of the computerized prediction of LN metastases are superior to those of radiological estimation techniques.

A meta-analysis of SLN mapping has shown a high detection rate (93.7 %) and an accuracy of 92 %; therefore, SLN mapping may help in avoiding unnecessarily radical dissections [11].

A single comparative study (SNB vs. MCP) from Germany has proven SNB to be of higher clinical relevance than the Maruyama computer model for predicting nodal status and compartmental involvement [25].

Although it is difficult to draw definitive conclusions in our prospective comparative study, owing to the small size of the series, we demonstrated a degree of reliability of MCP similar to that in the cited studies, with 91.3 % sensitivity, 64 % specificity and 80 % accuracy by the best cutoff point. The false-negative rate was 8.7 %. We detected SLNs in 97.4 % of patients with gastric cancer with 95.7 % sensitivity, and 100 % specificity using the blue dye-alone technique. The false-negative rate was 4.3 %—exactly half the false-negative rate found with MCP. We are planning to carry out reduced lymphadenectomy in SLN-negative patients in the near future, according to the internationally accepted guidelines.

As to the clinical meaning of the equivalence range (0.8–1.25 under general convention, subject to narrowing or widening if special circumstances justify) for the ratio of performance indicators in the given setting: perfect equivalence is represented by the value 1, while that part of the range greater than 1 represents the superiority of the Maruyama method over the SLN method (because all test performance indicators are formulated to express better performance with greater numerical values). The lowest point of the range represents the inferiority of the Maruyama method to an extent where it can only achieve 80 % of what SLN testing is capable of. For sensitivity, this means that, should this worst-case scenario be the actual case, 20 % of metastatic cases expected to be identified as positive through SLN testing are expected to be misclassified as negative by the Maruyama procedure. However, the point estimate is at a relative sensitivity of 0.955 (4.5 % fewer metastatic cases expected to be identified), and the confidence interval extends from 0.812 (18.8 % fewer cases identified) to 1.122 (12.2 % more cases identified; this presupposes an SLN sensitivity of 89.1 % or less, which is well within the 95 % confidence interval for that estimate). The analysis of other indicators produced no conclusive results, as the confidence intervals for the indicator ratios included values both inside and outside the equivalence range. So, the sensitivity of MCP and SNB was proven equivalent, while the specificity, NPV, PPV, and accuracy were higher with SNB.

It is generally accepted that metastases in SLNs indicate the need for a D2 lymphadenectomy. We analyzed the relevance of MCP in sentinel node-positive patients. The accuracy of MCP in sentinel node-positive patients was 16 % higher than that of SNB in our group of forty patients. The sensitivity and the PPV of MCP and SNB were proven equivalent in the sentinel node-positive group. Unfortunately, in this cohort of patients, the accuracy of MCP was low in the prediction of lymph node involvement in stations 7–12. So, it would be interesting in the future to find an appropriate technique that combines the sentinel node status and the results of MCP for determining the adequate extension of lymphadenectomy.

In summary, our comparative study showed a lower clinical impact of the MCP compared with that of SNB; however, using these two methods in a parallel fashion could be useful in preoperative decision-making for determining the appropriate extent of lymphadenectomy and individualized stage-adapted surgery in gastric cancer. The efficiency of MCP in the cohort of sentinel node-positive patients requires further evaluation.

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